UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,542	11/30/2001	John D. McNeish	PC10897ADAM	1000

7590 06/18/2003

Gregg C. Benson
Pfizer Inc.
Patent Department
Eastern Point Road, MS 4159
Groton, CT 06340

EXAMINER
BERTOGLIO, VALARIE E

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/006,542	MCNEISH ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *4,5 and 9-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 6-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of Group I as it relates to RAMP1 in Paper No. 17 is acknowledged. The traversal is on the ground(s) that a search of Group I would produce results for Group IV and would not require undue burden on the examiner. This argument is found persuasive and Groups I and IV will be rejoined. The traversal is on the ground(s) that a search of Group I and Group VII would not require undue burden on the examiner. This argument is not found persuasive. The protocols and reagents necessary to make the membrane preparation are distinct and separate from methods necessary to make the genetically modified animal. Furthermore, the animal and the membrane preparation have patentably distinct uses. Use of the animal and use of the membrane would require materially different protocols and technical considerations. Therefore, the requirement is still deemed proper and is therefore made FINAL.

Claims 1-14 are pending. Claims 1-3 and 6-8 as they pertain to the RAMP1 gene are under examination in the instant office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 6-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was

in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

Claims 1-3 encompass transgenic knockout mammals produced through gene-targeted insertion in somatic cells followed by generation of animals using somatic cell nuclear transfer in addition to the more traditional technique of homologous recombination in mouse ES cells followed by transplantation of the ES cell into a mouse blastocyst. The specification prophetically teaches the possibility of using homologous recombination in somatic cells followed by somatic cell nuclear transplantation to generate the claimed animals, however, it does not describe that this technique was actually used to generate the claimed animals or describe, to any degree, the phenotype of said animals. Due to the limited art available at the current time and at the time of filing, it is not clear that knockout animals produced by these two distinct methods would appear the same phenotypically. Fetuses generated by somatic cell nuclear transplantation, irrespective of whether they are genetically modified, are often abnormal and nonviable with no consistent pattern of abnormality to indicate the cause of the defects (Dinnyes, page 87, column 1, 3rd full paragraph; McCreath, paragraph bridging pages 1067 and 1068). Thus, it would be expected that phenotypes associated with the technique of somatic cell nuclear transfer, of unknown etiology, would arise independent of the phenotypes related to the gene knockout.

Since it is not realistic to expect that the "complete structure" of any transgenic animal can be described, the written description requirement is interpreted to be whether phenotypic consequences have been described. Due to the unpredictability in the art of making transgenic knockout animals and additionally in making animals by somatic cell nuclear transfer, it is not clear to one skilled in the art what the claimed animal would be. Given the limited information in

the specification, an artisan would not have been able to predict whether the animals generated by somatic cell nuclear transplantation would have had the same or different phenotypes compared to the animals generated by more traditional methods of homologous recombination in mouse ES cells. Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of all the genera encompassed by the claims.

Claims 6-8 encompass more than one RAMP1 gene as they recite "a disrupted RAMP1 gene". The claims encompass any RAMP1 gene that may exist in each and every species of animal. The specification teaches only one, mouse RAMP1 gene that comprises SEQ ID NO:1. Therefore, adequate written description to support the claims encompassing more than the one, disclosed RAMP1 gene is lacking.

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieve regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-3 and 6-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mouse or a cell whose genome comprises a homozygous disruption in the RAMP1 gene comprising SEQ ID NO:1 wherein said mouse exhibits altered liver and muscle function does not reasonably provide enablement for any species of transgenic non-human mammal with a disruption of any RAMP1 gene wherein said transgenic animal is heterozygous or has any phenotype. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-3 are directed to a genetically-modified, non-human mammal wherein the modification results in a disrupted RAMP1 gene. Claim 2 limits the mammal to a mouse. Claim 3 adds the limitation that the claimed mammal comprises an exogenous reporter gene under control of the RAMP1 promoter. Claims 6-8 are directed to a cell comprising a disruption in the RAMP1 gene. Claim 7 limits the cell to an ES cell. Claim 8 limits the cell to a mouse or human cell.

1) The specification fails to enable making and/or using any non-human species of mammal comprising a disruption of the endogenous RAMP1 gene wherein said mammal exhibits any phenotype or wherein said mammal is heterozygous for the gene disruption.

The art at the time of filing held that targeted gene insertion technology was not well-established for any species other than mouse. Since homologous recombination is required for gene targeting methods, cells in culture must be used to carry out the method. To generate a non-chimeric animal from the recombinant ES cells, the cells must be capable of contributing to the germ line. Campbell and Wilmut (1997, Theriogenology, vol. 47, pp, 63-72) acknowledge reports of ES-like cells in a number of species, but emphasize that as yet there are no reports of

any cell lines that contribute to the germ line in any species other than mouse (page 65). Other potential methods of generating transgenic embryos using homologous recombination were not fully developed at the time the invention was made (McCreath, 2000, Nature, Vol. 405, pages 1066-1069; Kent-First, 2000, Nature Biotechnology, Vol. 18, pages 928-929; Dinnyes, 2002, Cloning and Stem Cells, Vol. 4, pages 81-90). The first report of gene targeting in a lamb produced by somatic cell nuclear transfer of nuclei using fetal fibroblasts (McCreath, 2000) reported abnormal transgene expression/function. The first knockout lamb using this technique also met great difficulty (Denning, 2001, Nature Biotechnology, Vol. 19, pages 559-562). Furthermore, cloned fetuses, irrespective of whether they are genetically modified, are often abnormal and nonviable with no consistent pattern of abnormality to indicate the cause of the defects (Dinnyes, page 87, column 1, 3rd full paragraph; McCreath, paragraph bridging pages 1067 and 1068). It would be difficult to determine whether the phenotype resulting in a genetically modified animal generated by somatic cell nuclear transfer was a result of the genetic modification or an artifact of the nuclear transfer technique.

Furthermore, at the time of filing, the phenotype of transgenic knockout mice that are generated by any means, was unpredictable. Leonard (1995, Immunological Reviews, Vol. 148, pages 98-113) disclosed mice with a disruption in the g_c gene that was intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits (abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, line 7). Griffiths (1998, Microscopy Research and Technique, Vol. 41, pages 344-358) taught that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotypes (page 350, last paragraph). Thus, at the time of filing, ES cell-generated, gene-targeted animals had not be

prepared for any species other than mouse and the phenotype of any species of knockout animal generated via any method, including traditional gene-targeting using ES cells and somatic cell nuclear transfer, was unpredictable.

The specification teaches generating transgenic knockout mice by via insertional disruption of the endogenous mouse RAMP1 gene using homologous recombination in mouse ES cells. The specification teaches only prophetically, how one would generate a gene-targeted transgenic knockout mammal using cells other than ES cells (pages 25-26) and does not provide a working example or describe the resulting phenotype of any mammal generated by any method other than homologous recombination in mouse ES cells.

The specification fails to teach how one of skill in the art at the time of filing would generate a genetically modified mammal, including a mouse, comprising a disruption in the RAMP1 gene wherein the mammal has any phenotype as encompassed by the claims 1-3. Because the phenotype of transgenic animals is unpredictable, one of skill in the art would not know what phenotype to expect when making the claimed transgenic animal. Claims 1-3 fail to recite a phenotype and thus encompass any and all possible phenotypes. It would require one of skill in the art at the time of filing, undue experimentation to determine how to make and use any species of mammal comprising a genetic disruption of the RAMP1 gene wherein the mammal exhibits any phenotype as broadly claimed.

The specification fails to enable using a genetically-modified non-human mammal comprising a heterozygous disruption of the RAMP1 gene. The specification does not describe a phenotype for said mammal and thus, due to the unpredictability set forth by the art, it would not be clear to one skilled in the art how to make and use the mammal.

The specification further fails to enable disrupting <u>any</u> RAMP1 gene. Claims 1-3 and 6-8 refer to “a disrupted RAMP1” gene, which encompasses more than the single RAMP1 gene

disclosed in the specification. The specification only teaches one mouse RAMP1 gene (SEQ ID NO: 1) and does not indicate that there is more than one RAMP1 gene in any given mammalian species. The specification does not provide adequate guidance for determining any other RAMP1 gene or that other RAMP1 genes have the same function as the RAMP1 gene disclosed. Limiting claims 1 and 6 to a transgenic mouse or mouse cell and deleting "a" preceding "disrupted RAMP1" in claims 1 and 6 would overcome this rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear whether the claims are intended to encompass isolated cells in vitro or cells in vivo. If applicant is intending to claim cells in vitro, use of the term "isolated cells" is suggested.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1,2 and 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi (*Scientific American*, 1994, vol. 270, pp 34-41) in view of Hussman (Mol. Cell. Endocrin., 2000, Vol. 162, pages 35-43).

Capecchi taught a mouse and mouse ES cells whose genome comprised a disruption in the HoxA-3 gene by insertion of a selective marker gene into the HoxA-3 gene. Capecchi differs from the claimed invention in that the targeting construct does not disrupt the RAMP1 gene.

However, at the time the claimed invention was made, Hussman taught the nucleic acid sequence of the mouse RAMP1 gene (full text).

Accordingly, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to make a knockout mouse having a disruption in a targeted gene as taught by Capecchi wherein the gene was RAMP1 as taught by Hussman. One of ordinary skill in the art would have been sufficiently motivated to replace the Hox3A gene with the RAMP1 gene, as it was an art-recognized goal to determine the physiological role of a gene of interest by the generation of a knockout mouse. RAMPs are expressed in many different tissues at high levels, however, their role in these various cell types is not known. One of ordinary skill in the art would have been sufficiently motivated to disrupt the RAMP1 gene as a means of determining whether it has a role in regulating receptor systems other than the calcitonin receptor-like receptor.

Note that absent any phenotypic requirements for the claimed transgenic mouse, the combination of the cited prior art is sufficient to make obvious the claimed invention. Capecchi discloses the applicability of gene targeting to many other genes so that a correlation can be drawn between the malfunctioning gene and the manifestation of disease (page 41, column 2, 2nd full paragraph).

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on Mon-Weds 6:00-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Valarie Bertoglio
Examiner
Art Unit 1632

DEBORAH J. REYNOLDS
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600